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An Empirical Review of Major Legislation Affecting Drug Development: Past Experiences, Effects, and Unintended Consequences

AARON S. KESSELHEIM

Brigham and Women's Hospital; Harvard Medical School

Context: With the development of transformative drugs at a low point, numerous commentators have recommended new legislation that uses supplementary market exclusivity as an incentive to promote innovation in the pharmaceutical market.

Methods: This report provides an historical perspective on proposals for encouraging drug research. Four legislative programs have been primarily designed to offer market exclusivity to promote public health goals in the pharmaceutical or biomedical sciences: the Bayh-Dole Act of 1980, the Orphan Drug Act of 1983, the Hatch-Waxman Act of 1984, and the pediatric exclusivity provisions of the FDA Modernization Act of 1997. I reviewed quantitative and qualitative studies that reported on the outcomes from these programs and evaluated the quality of evidence generated.

Findings: All four legislative programs generally have been regarded as successful, although such conclusions are largely based on straightforward descriptive reports rather than on more rigorous comparative data or analyses that sufficiently account for confounding. Overall, solid data demonstrate that market exclusivity incentives can attract interest from parties involved in drug development. However, using market exclusivity to promote innovation in the pharmaceutical market can be prone to misuse, leading to improper gains. In addition, important collateral effects have emerged with substantial negative public health implications.

Conclusions: Using market exclusivity to promote pharmaceutical innovation can lead to positive outcomes, but the practice is also characterized by waste

Address correspondence to: Aaron S. Kesselheim, Division of Pharmacoepidemiology and Pharmacoeconomics, 1620 Tremont St., Suite 3030, Boston, MA 02120 (email: akesselheim@partners.org).

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and collateral effects. Certain practices, such as mechanisms for reevaluation and closer ties of incentives programs to public health outcomes, can help address these problems.

Keywords: Innovation, pharmaceutical, patent, legislation.

The U.S. pharmaceutical market has undergone a gradual change in the development of innovative therapeutics, with substantial implications for public health. Global rates of antibiotic resistance among bacteria continue to rise (Maragakis, Perencevich, and Cosgrove 2008), but in recent years, only five new systemic antibacterial agents have emerged from the largest pharmaceutical companies (Spellberg et al. 2008). Although tropical diseases remain a leading cause of mortality in low-income settings (Trouiller et al. 2002), they are managed primarily with products developed decades ago, which have important limitations (Nwaka and Hudson 2006). Even in fields like oncology, which has seen relatively high rates of new drug approvals (DiMasi and Grabowski 2007), many of the recent products have not substantially changed patient mortality, leading to questions about the usefulness or cost-effectiveness of such innovation (Denny, Emanuel, and Pearson 2007).

While some people blame the U.S. Food and Drug Administration (FDA) for stifling innovation (Miller and Conko 2007), clinical trial and regulatory review times today are short by historical standards (Keyhani, Diener-West, and Powe 2006), and the FDA's approval rates are consistently high for the products it evaluates (Sridhara et al. 2010). The low level of transformative drug production is related to a drop in new applications to the FDA for approval of innovative drugs. Paradoxically, this has occurred despite billions of dollars in public and private funding for research and development (R&D), as well as consistently high revenues reported by the pharmaceutical industry. As a result, diverse individuals have called for new federal policies to stimulate innovative drug development (Frantz 2006; GAO 2006; Rai et al. 2008).

Most such policy recommendations target the pharmaceutical industry's intellectual property environment, in which patents legally assign credit and ownership rights, allowing manufacturers to enforce market exclusivity. The development of new pharmaceutical products requires substantial up-front investment and technical knowledge. During the

patent-protected period, the manufacturer sets prices above the cost of production to recoup its financial investment and make a profit. When the market exclusivity time ends, generic versions may enter the market, and the resulting competition drives down prices. Generic drugs are less expensive in part because their manufacturers need to account for only the cost of drug synthesis and not the initial cost of R&D. Since nearly all generic drugs are clinically equivalent to the originals (Davit et al. 2009), they are widely substituted in clinical care (Shrank et al. 2010).

Thus, many proposals to promote pharmaceutical innovation use market exclusivity as a lever (Reichert 2003). The Government Accountability Office (GAO) recently suggested that patents could be lengthened "to 25 or 30 years" for important drugs with "high therapeutic potential," which would include certain antibiotic products (GAO 2006). This solution is likely to have a limited effect because net present value calculations heavily discount years far into the future. In 2008, the FDA Amendments Act authorized the sponsor of a new drug for a tropical disease to receive a transferable voucher entitling the company to expedited FDA review of a new drug application for any other product. By speeding up the FDA's evaluation time—and therefore providing earlier access to the market exclusivity period—the priority review voucher was projected to be worth $300 million to manufacturers (Ridley, Grabowski, and Moe 2006). In practice, however, the program had a rocky start. In April 2009, Novartis was awarded the first voucher for its antimalarial drug artemether-lumefantrine (Coartem) (FDA 2009). But since the product had already been developed and was in use outside the United States, Novartis was awarded the incentive without performing any new research into tropical diseases, which did not comport with the original goal of the legislation (Kesselheim 2008). Most recently, the Patient Protection and Affordable Care Act of 2010 enacted a system for approving follow-on biologic drugs (i.e., proteins or other large molecules derived from living cells), among which brand-name products have enjoyed little competition from bioequivalent alternatives even after their primary patents expired (Frank 2007). The final legislation also included twelve years of guaranteed market exclusivity for all biologic drugs (even if the drug's patent expired before that time). Anything less, industry advocates threatened, could hinder domestic innovation in biologic drugs (Wheadon 2010). The twelve-year exclusivity period, however, has been criticized as overly burdensome, and as a result, the viability of the new

pathway has been dismissed by potential follow-on biologic entrants (Gingery 2010).

Given the resurgence of interest in the United States in the legislative strategy of using market exclusivity to stimulate innovation, it is timely to examine the outcomes resulting from prior efforts, focusing on direct short- and long-term outcomes and collateral effects. This incentive strategy was prominent in four different pieces of legislation in the past thirty years: the Bayh-Dole Act of 1980, the Orphan Drug Act of 1983, the Hatch-Waxman Act of 1984, and the pediatric exclusivity provisions of the FDA Modernization Act of 1997. Here I describe studies that assessed the outcomes of these legislative programs and comment specifically on the studies' methodological rigor. The subjective tiering system that I used favors comparative studies and well-designed surveys over case studies and anecdotal reports, although the latter categories can generate important hypotheses and motivate policy changes.

The Bayh-Dole Act of 1980

In 1980, Congress adjusted intellectual property policy to encourage commercial development based on federal research funding. The University and Small Business Patent Procedures (Bayh-Dole) Act of 1980 gave U.S. small businesses and nonprofit organizations the authority to retain control of the patent rights in inventions arising from government-sponsored research and to offer exclusive licenses to private firms. Later, the statute's reach was expanded by executive order to include all government contractors.

The goal was to enhance commercial development by transferring intellectual property ownership from the government to the recipients of federal funding (So et al. 2008). Before Bayh-Dole, there was no consistent federal approach to managing inventions from government-sponsored research. Universities and the business community argued in the late 1970s that private control could encourage investment and more consistently bring the fruits of this research to market. They pointed to the poor record of licensing government patents for commercial development; that is, of the nearly 30,000 patents awarded to the government for inventions arising from federally funded research, only 5 percent were so licensed (GAO 1998). Notably, the 5 percent rate reflected a selection bias because it consisted largely of inventions by contractors

whose contracts with the government stipulated that they could have retained title to the patents if they had wanted to do so (Eisenberg 1996). In addition, the actual licensing rate was substantially higher for government-held patents in the biological sciences, in which 75 (23%) of 325 government-held health care–related patents were licensed as of 1976.

Studies Addressing Primary Outcomes of Bayh-Dole

Survey data have credited Bayh-Dole with promoting the licensing of federally funded work at U.S. universities. A survey of technology transfer office managers found that only 12 percent of university inventions were ready for commercial use at the time of license and that manufacturing feasibility was known only for 8 percent. The respondents believed that these early-stage discoveries would have remained undeveloped without exclusive license agreements with commercial sources (Jensen and Thursby 2001). Another survey of universities' technology transfer office managers reported that patenting practices were implemented in a manner to further the goal of technology commercialization (Pressman et al. 2006). In a GAO survey, nine out of ten business executives considered the legislation to be critical to their decisions to fund research in university settings (GAO 1987). Since 1991, the Association of University Technology Managers (AUTM) has conducted annual surveys of technology transfer offices regarding commercialization rates. In its 2008 report, the AUTM reported that 648 new commercial products had been created, 595 new companies formed based on university technology, and 5,039 total license and options executed (AUTM 2009a). These survey data, however, are limited by the respondents' biases, such as the social desirability response bias (see table 1). Manufacturers and technology transfer offices also have strong professional motivations to report positively on their commercialization activity.

Apart from survey data, counts of patents and technology transfer offices have demonstrated an association between the enactment of Bayh-Dole and enhanced patenting and licensing at research universities. The number of patents issued to the one hundred leading U.S. research universities more than doubled between 1979 and 1984 and more than doubled again between 1984 and 1989 (Mowery and Ziedonis 2000). In 1980, 390 patents were awarded to universities; by 2001, this number

TABLE 1
Selection of Studies Evaluating the Impact of the Bayh-Dole Act on University Patenting

Author(s)	Study Design	Summary of Most Important Outcomes
Blumenthal et al. 1997	Survey of life science faculty in 50 universities with highest NIH funding (2,167 respondents, 64% response rate).	Nearly 20% of respondents reported that publication of their research results had been delayed by more than 6 months at least once in the last 3 years for reasons including patent applications. Methodological comments: Moderate value. Large survey of active researchers that used rigorous methods.
Campbell et al. 2000	Stratified random sample survey of faculty in all U.S. medical schools (2,366 respondents, 62% response rate).	12.5% of respondents reported data withholding in the last 3 years. Methodological comments: Moderate value. Large, national survey with rigorous methods.
Jensen and Thursby 2001	Survey of licensing officers from 62 research universities about invention and licensing characteristics (1991–1995).	Respondents reported less than half of disclosed inventions were licensed (31% with exclusivity). Most university inventions required additional development before commercialization. Methodological comments: Low value. Relatively small survey and subjective report subject to response and recall bias.
Henderson, Jaffe, and Trajtenberg 2001	Comparison of subsequent citations of patents assigned to universities from 1965 to 1988 overall ("importance") and in other fields ("generality") vs. 1% random sample of all patents during this period.	There was a consistent increase in university patenting output during this time. University patent importance and generality grew in the 1970s, reached a plateau from 1975 to 1982, and fell from 1982 to 1988 (compared with a random sample). Methodological comments: Moderate value. Rigorous time-series analysis, but patent citations are of debatable relevance.

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TABLE 1—*Continued*

Author(s)	Study Design	Summary of Most Important Outcomes
Mowery et al. 2001	Descriptions of invention disclosure, patenting, and licensing activities in 3 university settings before and after Bayh-Dole Act.	After Bayh-Dole, the 2 universities active in patenting and licensing expanded marketing efforts, and the third initiated efforts to patent and market faculty inventions. Other factors contributed to these changes. Methodological comments: Moderate value. In-depth case analysis of 3 universities lacks generalizability, and the comparisons are descriptive.
Mowery and Ziedonis 2002	Descriptive and statistical comparison of patent-related activities in 3 university settings relative to one another and evaluation of a control set of university patents.	After Bayh-Dole, no decline in importance and generality of patents at these institutions, while a decline in "low intensity" patenting universities was noted. Methodological comments: Moderate value. Statistical comparisons done within the small sample and large sample; indirect comparisons done between samples.
Walsh, Cohen, and Arora 2003	Collection of interviews with intellectual property managers, researchers, and technology transfer officers.	Infringement of patents by university researchers is common but hard to detect and is tolerated by commercial entities. Methodological comments: Low value. Nonsystematic qualitative methods subject to possible biases; formal results not reported.

Mowery et al. 2004	Description of trends in university patenting before and after Bayh-Dole.	Consistent growth before 1980 in university share of patenting and patent propensity continued after passage of statute. Methodological comments: High value. Descriptive trend analysis with rigorous statistical comparisons.
Shane 2004	Comparison of share of patents assigned to universities across 117 lines of business from 1969 to 1996. Lines of business subcategorized based on qualities identified in survey of 650 technology managers.	Increase in university share of patents occurred in lines of business in which patent licensing is common, the biomedical sciences, real university research spending, and proportion of university research spending on "applied" science. Methodological comments: High value. Detailed time-series analysis using comparisons among lines of business.
Walsh, Cho, and Cohen 2005	Survey of biomedical researchers in noncommercial work (381 respondents, 92% response rate).	Respondents reported no work stoppages and rare delays related to patents. Methodological comments: Low value. No data on survey methods provided for independent analysis.
Sobolski, Barton, and Emanuel 2005	Description of reported net licensing income for 84 institutions (1996–2001).	A small number of highly profitable patents drive licensing revenues. The vast majority of institutions earn relatively little income with small-to-moderate research budgets. Methodological comments: Moderate value. Detailed comparison of trends among universities (all post–Bayh-Dole).

Continued

TABLE 1—*Continued*

Author(s)	Study Design	Summary of Most Important Outcomes
Murray and Stern 2007	Comparison of citations to articles published in *Nature: Biotechnology* (1997–1999) that were paired with a patent, relative to other citations.	The citation rate after the patent grant declined by 10% to 20%, providing some empirical basis for the anticommons effect. Methodological comments: Moderate value. Statistical comparison based on small sample size using indirect data.
Bulut and Moschini 2009	Evaluation of net licensing revenues in 148 universities, grouped according to descriptive characteristics (1998–2002).	The expected returns of the top 10% of earners remain a relatively small fraction of the total research expenditure of the universities. Modest returns on average from patenting and licensing practices. Methodological comments: Moderate value. Comprehensive comparison of university licensing practices (all post–Bayh-Dole).
Sampat 2009	Review of a cohort of 1,546 drug applications to FDA (1988–2005), supplemented by reviews of patents from Orange Book and other sources.	72 drugs had an academic patent associated with them and universities own patents on nearly 19.2% of the drugs that are arguably the most innovative. Methodological comments: Moderate value. Innovative examination of the role of academic research in developing important drugs.
Williams 2010	Analysis of the human genome sequencing by the public Human Genome Project and the private firm Celera, and estimate of impact of different strategies on outcomes.	Private intellectual property rights held by Celera had persistent negative effects on subsequent innovation on the order of 30%, based on reductions in subsequent scientific research and product development outcomes. Methodological comments: High value. Rigorous analysis of innovation rates using a fortuitous natural experiment in the field of DNA sequencing.

Stevens et al. 2011	Collection of successful drug-discovery and drug-development projects from reviews of federal reports, private industry reports, and trade association reports.	153 new FDA-approved drugs, vaccines, or new indications for existing drugs were discovered through research carried out in public service research institutions. Methodological comments: Moderate value. Most comprehensive list of academic-based research leading to marketed products, using internal data from the Association of University Technology Managers and the NIH Office of Technology Transfer.
Sampat and Lichtenberg 2011	Evaluation of intellectual property origins of sample of 478 drugs (approved NMEs 1998–2005).	Government funding played indirect role in nearly half of all drugs approved, including nearly 2/3 of all "priority review" drugs. Methodological comments: Moderate value. Comprehensive review of contributions at level of patent to drug development, including a comparator sample to assess relative contributions to more- and less-innovative drugs.

had increased to 3,203 (Schacht 2005). However, the trends reported cannot be definitively linked to causation, in part because these studies do not have control groups to suggest how Bayh-Dole might have differentially affected outcomes.

Industry funding of research at universities and industry-university partnerships increased after Bayh-Dole. The aggregate gross licensing revenue obtained by universities approached $1 billion in 2002 (AUTM 2002), and the number of universities with technology transfer offices rose from twenty-five in 1980 to two hundred in 1990 (Cohen et al. 1998). But as with patents, descriptive counts of technology transfer offices or gross licensing revenues are not fully reliable in helping define causation (Thursby and Thursby 2008). In addition, studies providing results at the institutional level paint a different picture from that of the aggregate reports of technology transfer offices. For example, one study specifically looked at the median net licensing income per institution for a sample of eighty-four major U.S. universities, hospitals, and research institutes, a value that subtracts legal expenditures and payments to other institutions from gross licensing income (Sobolski, Barton, and Emanuel 2005). The authors found that the median net licensing income per institution was only $1.13 million per year. There was also an uneven distribution of income, as 13 percent of the institutions earned more than $10 million per year, with the six highest earners (top 7%) accounting for nearly 60 percent of all income. Another analysis confirmed that only a few universities earned large returns and found that, overall, the expected licensing returns were modest, especially when compared with the investment in university research expenditures (Bulut and Moschini 2009). Both sets of researchers concluded that the resources allocated to some technology transfer offices might be better spent elsewhere, as costs may exceed revenues over time.

Other studies have tried to quantify Bayh-Dole's impact on product output. For example, one study found that universities increased their patenting after Bayh-Dole in lines of business in which licensing is an effective mechanism for acquiring technical knowledge. This work is persuasive because it compares differential effects of Bayh-Dole across industry sectors, and the author concluded that university research became more commercially oriented (Shane 2004). Another high-quality economic analysis concluded that Bayh-Dole helped spur centers of innovation and entrepreneurship (Hausman 2011). By contrast, Mowery and Sampat found that university patenting overall had begun

to grow before the Bayh-Dole Act (Mowery and Sampat 2001) and that "patent propensity" (defined as patents per dollar of academic research and development spending) grew steadily, with no sharp break in trend in 1980 (Mowery et al. 2004). To determine the causes of increased university patenting, a follow-up study examined intellectual property management at three leading academic institutions—Columbia University, the University of California, and Stanford University—and found substantial growth in patenting and licensing activities before Bayh-Dole (Mowery et al. 2001). These data, based on in-depth examinations of the three institutions, are limited primarily by a lack of generalizability.

A different research group sought to quantify the effect of Bayh-Dole on the quality of university patents. The investigators used a comprehensive database of university patents (1965 to 1988), compared to a 1 percent random sample of all patents issued during this period. Examining the subsequent citations received by these patents, they found a decline in the importance and generality of university patents relative to the random sample from 1982 onward (Henderson, Jaffe, and Trajtenberg 2001). They concluded that universities may have sought more patents on fewer important inventions. An alternative explanation is that the quality of patents after Bayh-Dole changed, owing to the entry of universities less savvy about the types of inventions to patent. A study of patents assigned to nearly all U.S. universities from 1975 to 1992 tested this hypothesis and found that those universities actively involved in patenting before Bayh-Dole demonstrated consistently high levels of patent importance throughout the study period (Mowery and Ziedonis 2002). But the patents produced after Bayh-Dole by universities that had rarely or never patented before the law's passage tended to be of low importance.

More recent studies looked beyond patents to pharmaceutical product output. In 2009, Sampat identified seventy-two drugs approved in the past twenty-five years whose patents point to involvement by academic inventors, including some of the most novel and clinically useful drugs produced during that time (Sampat 2009). Using a similar database, another study compared the patent origins of all new drugs approved between 1998 and 2005 and found that government funding played a role in almost half of the 478 products, including almost two-thirds of the most important or innovative ones (Sampat and Lichtenberg 2011). Similarly, Stevens and colleagues identified 153 new FDA-approved

drugs, vaccines, or new indications for existing drugs that were discovered through research carried out in public-sector research institutions (i.e., universities, research hospitals, nonprofit research institutes, and federal laboratories) and directly linked to federal funding (Stevens et al. 2011). These studies suggest that government-funded research contributes substantially to pharmaceutical development, but the results do not address whether Bayh-Dole or the licensing process was essential to the innovative work.

In fact, one study suggested that an open-source model might be more effective than a private licensing regime in spurring development. This study of output from DNA-based patents compared gene sequencing by the Human Genome Project with output from the private firm Celera to determine whether privately held intellectual property rights encouraged innovation (Williams 2010). Celera's methodology of assigning intellectual property to sequenced genes led to less future research and product development than did the public effort.

Studies Addressing Collateral Effects of Bayh-Dole

Commentators have expressed concern that Bayh-Dole has contributed to the web of patents encompassing the basic work in university settings, thereby slowing the progress of scientific investigation and raising the costs of biomedical research through licensing expenses, a hypothesis that has been termed the "tragedy of the anticommons" (Heller and Eisenberg 1998). Individual cases supporting this hypothesis exist; for example, biotechnology firms seeking to do research on stem cells have faced substantial fees and restrictive licensing strategies from the University of Wisconsin for using its patents covering embryonic stem cell lines (Holden 2007). Other commentators, however, argue that the rise in university patenting does not act as a barrier to progress in the biological sciences (Caulfield et al. 2006; Epstein and Kuhlik 2004).

Empirical data relating to the potentially negative effects of patents on university research have been mixed. One analysis of research paper citations found that the citation rate after the patent grant declined by 10 to 20 percent (Murray and Stern 2007). Surveys of life sciences researchers found that the filing of patent applications was associated with withholding data from dissemination in the scientific community

for six months or more (Blumenthal et al. 1997, Campbell et al. 2000). In a different survey of biomedical scientists, withholding data from colleagues was identified as a leading contributor to delays in the progress of science (Campbell et al. 2002).

By contrast, a different set of studies of biochemical scientists in university and industry settings did not find that work was slowed by competing patents or the need for licensing arrangements (Walsh, Arora, and Cohen 2003; Walsh, Cohen, and Arora 2003). For example, one reason that patents on others' research progress did not have a negative impact was that research scientists did not "pay much attention to others' patents" (Walsh, Cho, and Cohen 2005). These studies, which included limited surveys as well as a report of self-selected interviews, also did not report a link between patenting and keeping their research secret (Walsh and Hong 2003). The researchers concluded that the "tragedy of the anticommons" effect was not substantial, although the survey methods used here were much more limited in scope and much less rigorous than the national studies of biomedical researchers conducted by Blumenthal and Campbell and their colleagues.

Conclusions about Bayh-Dole and Recommendations for Future Research

After Bayh-Dole, patenting and licensing at U.S. universities grew, but the magnitude of the legislation's contribution is not known because the evidence indicates that an increase in this activity was already under way. Collateral effects, such as a change in academic research culture, may have had important implications as well. From this review of the literature, the following three areas of inquiry related to Bayh-Dole and its effect on pharmaceutical development remain open for more rigorous evaluation:

- The relationship between academic patenting and innovation either in drugs or in basic science discoveries directly linked to subsequent therapeutic product development.
- The effects of academic patents on collaboration, secrecy, and research costs.

- The role of academic technology transfer offices in fostering drug development, including the use of strategies such as exclusive licensing.

One source for funding such research could be the National Institutes of Health (NIH), a leading source of federal grant funding and the organization charged with ensuring that the resulting intellectual property in the biomedical sciences is properly managed (Sampat and Lichtenberg 2011). The NIH's director, Francis Collins, recently announced the creation of a new institute to enhance drug development, called the National Center for Advancing Translational Science (NCATS) (Collins 2011). Because one goal of the NCATS is to support drug development through its risky early stages, supporting research to identify the utility of the patenting and licensing process would complement its mission. While the most convincing work to date has focused on patent rates and trends, the overall effectiveness of Bayh-Dole can also be evaluated by investigating how government and academic resources contribute to the development of the final products of biomedical research, including pharmaceutical agents.

In addition, we have little information to guide academic licensing policies in ways that promote public health benefits. For example, nonexclusive licensing has been offered as a way to promote access to drugs and related technologies in low-income settings (Kapczynski et al. 2005), and some academic centers have considered changing their licensing practices (AUTM 2009b). Even though the effects of such changes might take some time, they should be empirically evaluated. This research should be supported by groups like AUTM and could include, for example, a comparative review of internal licensing strategies followed by academic institutions.

Finally, on the issue of collateral effects, more work should evaluate the "tragedy of the anticommons" hypothesis and its relevance to pharmaceutical development. As a starting point, academic researchers should be surveyed to follow up on Blumenthal's early work. These surveys should evaluate both the subjective attitudes of basic scientists toward intellectual property and technology transfer, as well as their behaviors toward collaboration and licensing. In recent years, pharmaceutical industries have made progress in developing relationships with academic researchers to support their work in drug development, so the parameters of these relationships should also be explored.

The Orphan Drug Act of 1983

In 1983, Congress passed the Orphan Drug Act, the first market-based incentive program aimed at a particular class of diseases. This legislation applied to treatments for conditions for which there was "no reasonable expectation" that U.S. sales could support the drug's development (it was later amended to apply as well to disease with a prevalence of less than 200,000). The Act provides three primary incentives: (1) federal grants and contracts to support clinical trials of orphan products, (2) a tax credit of 50 percent of clinical testing costs, and (3) an exclusive right to market the orphan drug for the approved use for seven years from the date of marketing approval. Orphan drugs may be granted fast-track status for FDA reviews, and user fees commonly paid to the FDA by manufactures are waived. The Orphan Drug Act applies to both new drugs and off-patent or already-marketed drug products.

The Orphan Drug Act's market exclusivity provision resembles a patent, although it derives its significance to manufacturers because the seven-year period starts on the date of the FDA's approval. This is a powerful incentive because it is not based on the validity or scope of any patents protecting the underlying compound and begins only when the drug is approved (unlike patents, which are usually obtained during the preclinical testing period). The FDA can approve a clinically superior product that has the same active ingredient before the expiration of seven years, although this has never happened in practice. In addition, orphan exclusivity applies only to the FDA-approved indication. Competitors may therefore develop the same product (if it is not patent protected) and conduct clinical trials for other indications, although the diminishment of the potential market from the orphan designation may discourage such a strategy.

Studies Addressing Primary Outcomes of the Orphan Drug Act

Counts of drug production and investment after the Orphan Drug Act was passed are common. In the decade before 1982, the FDA approved only ten treatments for conditions later defined as orphan diseases (Haffner 2006). By 1988, fourteen research-intensive pharmaceutical manufacturers reported having invested nearly $200 million in

orphan drug–related research (NIH 1988). From 1983 through 2009, the FDA's Office of Orphan Products Development (OOPD) assigned a total of 2,113 orphan designations. The FDA approved 347 total orphan drugs, including 279 distinct products (some drugs were approved for more than one orphan indication) (Kesselheim 2010a). An OOPD review found that the number of orphan drugs has increased as a percentage of all drug approvals, from 17 percent (1984–1988) to 31 percent (2004–2008), and was 35 percent in 2008 (Coté et al. 2010). Orphan products now represent about one-third of FDA-approved drugs and biologics (Wellman-Labadie and Zhou 2010).

Such descriptive studies have limited utility, however, in part because no effort is made to account for confounding factors that might have contributed to the results. For example, orphan drugs can produce substantial profits for their manufacturers. One early study determined that the eleven top-selling orphan drugs each earned more than $200 million within five years of being marketed (Peabody, Ruby, and Cannon 1995). A recent analysis also showed that orphan drugs faced less profit-reducing generic competition overall than did nonorphans (Seoane-Vazquez et al. 2008). Such results suggest that characteristics of the drug reimbursement system in the United States that permit high prices for certain types of medications may have inspired at least some orphan drugs to be developed without the orphan drug designation.

Other, more rigorous, studies have tried to assess the impact of the Orphan Drug Act. Heemstra and colleagues examined publications related to a cohort of rare diseases to assess scientific output before and after the Orphan Drug Act was enacted (1976–2007) (Heemstra et al. 2009). They found that the rise in publications was not statistically different from the rise in scientific publications overall during that period, suggesting an inconclusive role for the legislation in stimulating rare disease research worldwide. Two economic studies also provide convincing evidence regarding the impact of the Orphan Drug Act. In one, Yin compared a set of control diseases with rare diseases to estimate the impact of the legislation on new clinical trials. He found a 69 percent increase in the annual flow of clinical trials for drugs for rare diseases, net any increases in the rate of new clinical trials for control diseases (Yin 2008). But he also found a differential effect on innovation, with the greater effect among orphan drugs with higher disease prevalence and thus greater market potential. In a second study, Yin found that the Orphan Drug Act encouraged manufacturers to target subdivisions

of nonrare conditions, such as subpopulations that are refractory to existing therapies or have a severe or progressed form of a disease. Such strategic positioning might be socially useful; indeed, Yin notes "the development of personalized drugs that treat narrowly defined subsets of patients within broadly defined disease populations is widely thought to be a promising direction for future drug research" (Yin 2009, 961). Other anecdotal reports question the utility of the Orphan Drug Act's incentives when the orphan products would otherwise have been developed for larger populations (Arno, Bonuck, and Davis 1995). The OOPD seeks to prevent such "salami slicing" by permitting the orphan designation for only "medically plausible" subsets of diseases (Maher and Haffner 2006).

Studies Addressing Collateral Effects of the Orphan Drug Act

Secondary concerns have arisen with the implementation of the Orphan Drug Act. If the Orphan Drug Act does encourage the market positioning of products that might otherwise have been tested and approved for a larger population, this is a dangerous outcome, for two reasons. First, premarketing studies of orphan drugs tend to enroll extremely small numbers of patients. For example, in the case of alglucerase (Ceredase), a treatment for Gaucher's disease, a rare congenital enzyme deficiency, the manufacturer spent less than $60 million developing the drug, earning approval primarily on the basis of a one-year randomized controlled trial involving twelve patients (Goldman, Clarke, and Garber 1992). The studies leading to the FDA's approval of orphan drugs also tend to lack basic features of high-quality clinical trial design. Comparing orphan and nonorphan drug approval in the field of neurology, one set of authors found that orphan drugs were less likely to be approved on the basis of two randomized, double-blind placebo controlled trials (32% v. 100%, $p < 0.001$) (Mitsumoto et al. 2009). Similar results were found in the field of oncology (Kesselheim, Myers, and Avorn 2011). Pivotal trials for orphan cancer drugs enrolled substantially fewer patients than did trials for nonorphan cancer drugs (median 96 v. 290, $p < 0.001$) and were less likely to be randomized (30% v. 80%, $p = 0.007$) or double-blinded (4% v. 33%, $p = 0.04$). The higher frequency of nonrandomized, nonblinded trials of orphan drugs raises questions about the robustness of

the findings of such trials, particularly if the orphan drugs are then prescribed off-label to a larger population.

In addition, if early studies of orphan drugs leading to FDA approval necessarily involve only small numbers of patients, safety issues may arise for orphan drugs after approval. Kesselheim and colleagues found that newly approved orphan cancer drugs had higher odds of serious adverse events in their pivotal trials than did nonorphan cancer drugs (1.72 [95% CI: 1.02–2.92, p = 0.04]). An early government-led analysis suggested that 31 percent of orphan drugs on the market had demonstrated more pronounced side effects during preapproval clinical testing than did nonorphan drugs, and following FDA approval, 13 percent produced more side effects than anticipated (Scharf 1989). By contrast, a more recent cohort study of approved orphan drugs found that the probability of a first safety-related regulatory action was slightly lower among orphan drugs for both biologic products and new molecular entities overall, although orphan drugs approved on a shorter time frame by the FDA may have a higher risk for a safety-related regulatory action (relative risk [RR] 3.32; 95% CI 1.06–10.42) (Heemstra et al. 2010). If orphan drugs are approved with outstanding safety issues, this is particularly problematic for orphan drugs that end up being used widely off-label. For example, erythropoeitin alpha (Epogen) was approved as an orphan drug in 1989 to treat anemia associated with end-stage renal disease but was prescribed for patients with all types of anemia (Walton et al. 2008). Recently, the use of erythropoeitin was greatly reduced after studies linked the product to increased cardiovascular mortality (Singh et al. 2006).

Finally, studies have highlighted rare diseases that the Orphan Drug Act may not adequately reach because it seems to disproportionately encourage the development of drugs with a viable U.S. market (Trouiller et al. 1999). Only seven orphan drugs approved in the United States have been intended for use in neglected tropical diseases (five of which were AIDS-related infections) (Villa, Compagni, and Reich 2009). Heemstra and colleagues looked at rare disease development as well and found that a disease with a prevalence between 10 and 50 per 100,000 had a more than threefold higher chance of obtaining at least one product with an orphan drug designation (adjusted OR = 3.72; 95% CI = 1.37–6.44) than did a disease with a prevalence of 0.1–0.9 per 100,000. They concluded that "current orphan drug legislation alone is not sufficient to stimulate orphan drug development for diseases with a very low prevalence" (Heemstra et al. 2009, 1166).

Conclusions and Recommendations for Future Research on the Orphan Drug Act

The most methodologically rigorous studies of the Orphan Drug Act indicate that there was a response to the incentives offered by this legislation, whereas other market forces, such as anticipated revenue, may also have affected orphan drug development (see table 2). While the importance of the Orphan Drug Act should not be understated for its success in making increased resources available for rare disease drug development, the cost-effectiveness of the incentives remains unknown. Investigators should address whether public resources should be distributed to favor orphan drugs with greater overall public health importance because the disease is more debilitating or there are no other legitimate treatment options available. For example, in 2010, the FDA approved velaglucerase-alfa (Vpriv) as an orphan-designated drug for the treatment for Gaucher's disease to compete with alglucerase. A case study of the economics of the Gaucher's disease market would help explain how such a rare condition could support the introduction of a follow-on product and how the Orphan Drug Act played a role in the development of this competing drug. Additional research is also needed about the use of orphan drugs after approval, for example, to determine when orphan drugs are widely used off-label. Such work could help address the concerns about market positioning related to orphan drug designation.

Finally, more cross-national comparative research may be useful, as Heemstra and colleagues have already done with admirable success. The European Union (EU) passed similar legislation in 2000 providing a ten-year exclusivity period (Cabri and Tambuyzer 2001). But the EU program oversaw the approval of only fourteen new drugs in its first five years, and many of those approvals were provisional and based on incomplete data (Joppi, Bertele, and Garratini 2006). Comparisons of different environments may provide the basis for controlled studies and some insight into how manufacturers respond to incentives in this field.

The Hatch-Waxman Act

With the Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984, Congress sought to encourage innovation by both brand-name and generic drug manufacturers. Clinical testing periods, as well as FDA review time, increased during the 1960s and 1970s, so

TABLE 2
Studies Evaluating the Impact of the Orphan Drug Act on Drug Development

Author(s)	Study Design	Summary of Most Important Outcomes
Shulman et al. 1992	Descriptive analysis of 8 years of orphan drug activity (1983–1991).	They found 440 orphan drug designations encompassing 254 different drugs and reported on 32 different variables, sales data, and FDA review times. They found few differences between high-sales and low-sales products. Methodological comments: Moderate value. Large amount of important data reported relevant to assessing Act's early success, but no statistical comparisons.
Goldman, Clarke, and Garber 1992	Case report of development of algucerase (Ceredase) for Gaucher's disease.	They conducted detailed investigations of the development of products, including role of federal funding and the act. Methodological comments: Low value. Case reports are useful for generating hypotheses.
Arno, Bonuck, and Davis 1995	Case report of application of Orphan Drug Act to AIDS-related drug development.	They documented examples of off-label use of orphan drugs and substantial profits for manufacturers in rare–disease market. Methodological comments: Low value (case report).
Shulman and Manocchia 1997	Descriptive analysis of 13 years of orphan drug activity, including FDA review times (1983–1995).	They found 631 orphan designations involving 450 different drugs. 26% of orphan-designated drugs had prior FDA approval. Methodological comments: Moderate value. See prior Shulman study.

Trouiller et al. 1999	Descriptive analysis of orphan drug approvals focusing on drugs for tropical diseases.	Of 152 orphan drugs approved, 3 were for malaria or trypanosomiasis. Methodological comments: Low value. Descriptive analysis of subpopulation of orphan drugs.
Office of the Inspector General 2001	Descriptive analysis of orphan drug approval and disease prevalence, interviews with orphan disease manufacturers and patient advocacy groups, focus groups with FDA, and consults with drug policy experts.	They found that the act's incentives motivate drug development, that orphan drugs are generally available to patients, and that the OOPD is a useful resource to manufacturers. Methodological comments: Low value. Nonsystematically collected interview data.
Lichtenberg and Waldfogel 2003	Ecological comparison of claims data on disease prevalence, drug use, and longevity before and after the act.	There was growth in prescription drug consumption among low-prevalent illnesses and decrease in mortality, in comparison with high-prevalent conditions. Methodological comments: Low value. Analysis provides possible evidence of associations but no evidence of causation.
Joppi, Bertele, and Garattini 2006	Descriptive analysis of orphan drug designation and approval in Europe (2000–2004).	In Europe, there were 255 orphan designations, and 18 (7.1%) approvals. Of approved products, 10 (56%) were approved when the clinical trials were not complete, and randomized controlled trials were performed for 9 (50%). Only 1 drug was tested against active comparators. Methodological comments: Moderate value. Descriptive study with no comparison group.

Continued

TABLE 2—*Continued*

Author(s)	Study Design	Summary of Most Important Outcomes
Yin 2008	Comparative analysis of rates of new clinical drug trials for orphan and uncommon (nonorphan) diseases (1981–1994).	There was a 69% increase in flow of new clinical trials for drugs for primary rare diseases. Innovation for diseases of smallest prevalence limited to years immediately following statute; innovation for orphan diseases with higher prevalence was sustained throughout study period. Methodological comments: High value. Detailed statistical comparisons and modeling based on comprehensive databases of orphan drugs and clinical trials, with internal comparisons based on disease prevalence.
Seoane-Vazquez et al. 2008	Descriptive analysis of orphan designations (1983–2007) and subsequent market activity; statistical comparison with nonorphan new drugs.	A large number of small sponsors have participated in the program. Orphan drugs had significantly less generic competition ($p < 0.001$). Orphan exclusivity increased maximum effective exclusivity by average of 0.8 years ($p < 0.001$). Methodological comments: High value. Comprehensive data collection and valid statistical testing on relevant criteria between orphan and nonorphan drugs.

Heemstra et al. 2009	Review of orphan drug approvals, prevalence figures, and scientific publications overall (1976–2007).	Increase in publications related to orphan diseases is not statistically different from the general trend. Higher-prevalence orphan diseases had a more than threefold higher chance of obtaining at least one product with a designation (adjusted OR = 3.72; 95% CI = 1.37–6.44) than did lower-prevalence diseases. Rare diseases with a high number of scientific publications are more likely to obtain a product with an orphan designation than are rare diseases with a low number of publications. Methodological comments: High value. Comprehensive data collection and novel comparison with scientific publications.
Yin 2009	See prior Yin study.	There were significant increases in clinical trials for subdivisions of nonrare diseases that would qualify for the Orphan Drug Act. Methodological comments: High value. See prior Yin study.
Wellman-Labadie and Zhou 2010	Descriptive analysis of approved orphan drugs (1983–2009), with subcategorization based on drug, disease, and manufacturer.	Orphan drugs were most often approved for oncology-related uses. At least 9% of orphan drugs have reached "blockbuster" status. Methodological comments: Moderate value. Substantial descriptive data in this comprehensive analysis but no comparison testing.

Continued

TABLE 2—*Continued*

Author(s)	Study Design	Summary of Most Important Outcomes
Heemstra et al. 2010	Cohort study of approved orphan drugs (2000–2008) examining the following outcomes: nature, frequency, and timing of safety-related regulatory actions, defined as (1) safety withdrawals, (2) "black-box" warnings, and (3) written communications to health care professionals issued by the U.S. FDA or the European Medicines Agency.	The probability of a first safety-related regulatory action for orphan drugs was 20.3% after 8 years of follow-up, similar to rates of nonorphan drugs. Higher-risk subclasses of orphan drugs include those approved by accelerated approval (relative risk [RR] 3.32; 95% CI 1.06, 10.42), oncological products (RR 7.83; 95% CI 0.96, 63.82) and products for gastrointestinal and metabolism indications (RR 10.44; 95% CI 1.25, 87.27). Methodological comments: Moderate value. Well-conceived cohort study, although outcomes assessed have limitations.
Coté et al. 2010	Descriptive analysis from internal FDA OOPD data of all orphan drug approvals (1983–2008).	Orphan products now represent roughly one-third of all FDA's newly approved drugs and biologics. Methodological comments: Moderate value. High-value internal data but limited results presented and comparisons drawn.
Heemstra et al. 2011	"Case-control" design using 41 approved orphan drugs as cases and 15 unapproved drugs as controls (1998–2007).	Study identifies two characteristics of successful orphan drug applications: the choice of the primary end point and target population of a pivotal clinical trial for an orphan drug and the experience of the company conducting the trials. Methodological comments: Moderate value. Superb analysis using internal FDA data, although sampling strategy for controls is debatable.

Kesselheim, Myers, and Avorn 2011	Comparative analysis of orphan and nonorphan drug approval in oncology (2004–2010).	Orphan cancer drugs had a shorter (but not statistically significant) clinical development time (median 5.1 vs. 6.9 years, $p = 0.07$). Pivotal orphan drug trials enrolled fewer patients (median 69 vs. 290, $p < 0.001$) and were less likely randomized (30% vs. 80%, $p = 0.007$) and double-blind (4% vs. 33%, $p = 0.04$). More treated patients had serious adverse events in orphan drug studies (OR 1.72; 95% CI 1.02–2.92, $p = 0.04$). Methodological comments: Moderate value. Analysis of primary FDA data, but small numbers of drugs overall and potential differences in underlying comparators.

at that time, new brand-name products had approximately an average of 8.1 years remaining on the drug's twenty-year patent term after FDA approval (Grabowski and Vernon 2000). In addition, in the years leading up to Hatch-Waxman, the generic drug market had lagged, with generics accounting for only 19 percent of all prescriptions (CBO 1998) and about 150 brand-name drugs lacking generic versions, despite being off-patent.

In the brand-name market, Congress responded to concerns about the increasing time of drug development with the Patent Term Restoration program. The Hatch-Waxman Act authorized extending the term of a drug patent to compensate for the premarket development time. The length of the extension for a given drug was the duration of the FDA review before approval, plus half the time for clinical trials. The extension could not exceed five years (two years for products already in the pipeline [Lourie 1989]), and the total patent term plus any restoration extension could not exceed fourteen years from FDA approval.

At the same time, to promote competition with generic drugs for off-patent products, Hatch-Waxman permitted generic products to be approved based on studies showing bioequivalence to the brand-name version (previously they had been required to conduct extensive human trials). Hatch-Waxman also gave generic manufacturers the opportunity to challenge brand-name patents and bring their bioequivalent products to market starting five years after the brand-name drug was approved (a so-called Paragraph IV challenge), although brand-name manufacturers could add 2.5 or more years of protection by contesting the Paragraph IV challenge. A Paragraph IV challenge could arise if the generic manufacturer claimed it had "designed around" the brand-name manufacturer's patents—thereby creating a bioequivalent product with the same active ingredient that did not infringe on any patents held by the brand-name company—or if the generic manufacturer claimed that the brand-name drug's patents were inappropriately granted by the U.S. Patent and Trademark Office. If the brand-name company contested the Paragraph IV challenge with a lawsuit, the resulting litigation would then evaluate the generic manufacturer's claims and determine whether the market exclusivity period could continue. As an incentive to generic drug manufacturers to bring a successful Paragraph IV challenge, the Hatch-Waxman Act offered 180 days of generic market exclusivity. The 180-day provision would lead to a market duopoly for a six-month period, allowing the generic manufacturer to keep prices

temporarily elevated and enhancing the generic manufacturer's revenue. Thus, Hatch-Waxman used a market exclusivity incentive to encourage generic manufacturers to either (1) bring their bioequivalent products to market sooner by designing around brand-name manufacturers' patents or (2) shoulder the expense of litigation to invalidate patents that were protecting brand-name drugs (Engelberg 1999).

Studies Addressing Primary Outcomes of Hatch-Waxman

Brand-Name Market. Brand-name manufacturers realized substantial market exclusivity extensions from patent term restoration (see table 3). The average patent restoration term was calculated to be 1.9 years for drugs approved between 1984 and 1986 and three years for drugs approved between 1993 and 1995 (Shulman, DiMasi, and Kaitin 1999). Grabowski and Vernon found that the average post-FDA approval patent term for new drugs was 11.8 years for a cohort of drugs introduced between 1991 and 1993, including an extension of 2.3 years (Grabowski and Vernon 1996). These results were consistent with a government study that calculated an average of 2.8 years of extensions (CBO 1998). Patent term restoration has contributed to an overall market exclusivity for new molecular entities that ranges from about 12.6 to 15.9 years, with higher-selling drugs usually on the lower end of that spectrum (Grabowski and Kyle 2007). Other contributors to longer market exclusivity terms after Hatch-Waxman include a reduction in FDA review times and efforts by brand-name companies to obtain additional patents on their drugs that serve as roadblocks to the entry of generics (Seoane-Vazquez, Schondelmeyer, and Szeinbach 2008).

Generic Market. Although Hatch-Waxman has been credited with helping create the currently thriving generic drug industry, the role of the 180-day generic exclusivity incentive is not clear (see table 4). From 1984 to 1989, only 2 percent of petitions to the FDA for generic drug approval contained a Paragraph IV challenge, but from 1990 to 1997, the number increased to 12 percent (FDA 1998). During those years, only three generic manufacturers received 180-day exclusivity periods (FTC 2002). By 2000, the rate of generic prescribing in the United States had already reached 50 percent; thus, the 180-day period did not aid the early generic drug boom.

TABLE 3
Studies Evaluating the Impact of the Hatch-Waxman Act on Brand-Name Market Exclusivity Term

Author(s)	Study Design	Summary of Most Important Outcomes
Grabowski and Vernon 1996	Descriptive analysis of prescription rates and sales prices for sample of brand-name products exposed to generic competition from 1989 to 1993, compared with similar samples from earlier periods.	The average effective patent term increased from 8.1 years on average in 1980–1984 cohort to 11.8 years on average in the 1991–1993 cohort. There was considerable variability in the average patent term. Methodological comments: Moderate value. Descriptive analysis on a small sample size.
CBO 1998	Descriptive analysis of sales and revenue data for 67 drugs approved between 1980 and 1984.	Generic market changes decreased returns on marketing new drugs about $27 million on average, roughly 12% of total average returns. Methodological comments: Moderate value. Descriptive comparison of changes in pharmaceutical market before and after statute.
Shulman, DiMasi, and Kaitin 1999	Descriptive analysis of patent term restoration for different cohorts of drugs exposed to generic competition from 1984 to 1995.	The mean restoration time increased steadily to an average of 3.0 years in the 1993–1995 cohort. The average effective patent term over study period was 11.0 yrs (range, 9.0–12.2). Methodological comments: Moderate value. Descriptive analysis but helpful stratification and comparisons across strata.

Grabowski and Kyle 2007	Review of market exclusivity periods for 251 drugs that first experienced generic competition from 1995 to 2005.	Since Hatch-Waxman, an increasing number of drugs face generic entry, including drugs with modest annual average sales. Average market exclusivity periods fluctuate from 12 to 15 years, with terms slightly lower for high-revenue products. Methodological comments: Moderate value. Systematic analysis with presentation of data trends. Authors find differential effect of Hatch-Waxman on top-selling drugs.
Seoane-Vazquez, Schondelmeyer, and Szeinbach 2008	Descriptive review of exclusivity periods of 340 new drugs approved from 1980 to 1999.	There was an increase in postapproval exclusivity time from 2.4 to 2.8 years on average, predominantly due to decrease in FDA review time. Methodological comments: Moderate value. Comprehensive analysis of new drug approvals with attempt to account for confounding factors.

TABLE 4
Studies Evaluating the Impact of the 180-Day Exclusivity Provision and Paragraph IV Challenges

Author(s)	Study Design	Summary of Most Important Outcomes
FTC 2002	Case studies of drugs from 1992 to 2001 in which generic competitor sought to challenge brand-name exclusivity period.	Numerous examples of cases in which brand-name competitor strategically attempted to delay generic entry. Methodological comments: Low value. Case studies are good for hypothesis generation.
Higgins and Graham 2009	Descriptive analysis of Paragraph IV challenge rates.	There was a marked rise in Paragraph IV challenges since 2001. Methodological comments: Low value. Brief, descriptive report.
Liebowitz 2009	Economic calculation of projected cost-saving based on rates of settlement agreements in last 4 years and average cost of generic competition delay during that time.	They predict that $35 billion in savings would be realized over the next 20 years if anticompetitive Paragraph IV challenge settlements were banned. Methodological comments: Moderate value. Rigorous attempt to quantify cost of 180-day exclusivity, but sensitivity analysis showed considerable variability in estimates.
Hemphill and Sampat 2011	Analysis of Paragraph IV challenges and market entry for drugs that first experienced generic competition from 2000 to 2010.	They find a higher rate of Paragraph IV challenges but no change in effective market exclusivity during the decade studied. Paragraph IV challenges play a restorative role, targeting weak and later-issued patents that might inappropriately extend market exclusivity. Methodological comments: High value. Comprehensive analysis of market exclusivity, patents, and generic entry. Implications include concern about anticompetitive settlements of Paragraph IV challenges.

As generic prescriptions have since risen to account for more than 70 percent of the market (and only 20 percent of the spending on prescription drugs), the number of Paragraph IV challenges markedly increased from 35 in 2001 to 165 in 2008 (Higgins and Graham 2009). Yet this rise has not been accompanied by similar trends in granting 180-day exclusivity periods, overturning invalid patents, or earlier introduction of generic drugs. Indeed, more generic manufacturers have ended litigation arising from Paragraph IV challenges in exchange for lucrative settlements, leaving the disputed patents in place (Hemphill 2006). The Federal Trade Commission (FTC) initially considered such agreements to be anticompetitive until it was overruled in 2005 by two federal Circuit Courts of Appeal. Since then, the number of Paragraph IV challenge settlements involving a restriction on generic entry and a payment from the brand-name to generic company ballooned from three to thirty-three in 2010 (Kesselheim, Murtagh, and Mello 2011). An FTC economic study concluded that U.S. consumers would save $35 billion over the next decade by preventing such arrangements, but this value is based on numerous assumptions related to the length of delay and sales of drugs. Varying the assumptions in a reasonable sensitivity analysis changed the estimate from as low as $6 billion to as high as $75 billion (Liebowitz 2009).

Conclusions and Recommendations for Future Research about Hatch-Waxman

Hatch-Waxman patent term restoration appears to have increased market exclusivity for brand-name drugs, although the shorter FDA review time and other confounders may limit a precise quantification of its effect. Still, no evidence has linked market exclusivity extensions arising from patent term restoration to enhanced innovation in the drug market by brand-name manufacturers and the development of additional novel products. It has been said that patent expiration is a greater driver of innovation and development than are extended monopolies, but few independent researchers have attempted to address this question by examining pharmaceutical investment and production trends.

In the generic market, the impact of the 180-day exclusivity period is controversial. Its availability, at least in recent years, may have attracted more generic manufacturers to the U.S. drug market, but a rising

number of challenges have led to settlements that have kept generics out and have not resulted in their earlier entry. This outcome is not consistent with the goals of that aspect of the legislation. Additional investigation of the 180-day market exclusivity period should be a top research priority. An excellent recent study by Hemphill and Sampat revealed the characteristics of patents for which Paragraph IV challenges were more likely, finding that the core patents on drug active ingredients tended to be spared while weaker, later-issued patents were more likely to be scrutinized (Hemphill and Sampat 2011). Still, there are no well-controlled studies of the economic impact of Paragraph IV challenges and the effect of settlements on drug availability and public health outcomes. Notably, Congress is considering a legislative adjustment to the 180-day exclusivity incentive. The influence of any such legislation on trends in this field should be closely monitored.

The Pediatric Exclusivity Extension

Due to their different body types and developing renal and circulatory systems, pediatric patients respond to drugs differently than do adults. Physiological variations in pediatric patients thus may enhance the risks, or reduce the benefits, of a drug. Because pediatric patients make up a minority of prescriptions of most drugs, companies have little financial incentive to organize or fund studies to guide prescribing (Wilson 1999). If prescription drugs were used in pediatric patients without supporting clinical trials, children may have received treatments that were underdosed, ineffective, or even dangerous (Szefler et al. 2003).

In response, the FDA asked manufacturers to voluntarily conduct clinical trials in pediatric patients, but with little success. Between 1990 and 1997, the dosing, safety, and efficacy of only eleven agents were sufficiently tested to warrant labeling changes regarding their applicability to pediatric patients (Baker-Smith et al. 2008). As a result, in 1997, legislation was enacted that offered drug manufacturers six months of market exclusivity time, starting at the end of the drug's patent-protected period, in exchange for conducting pediatric studies. The pediatric exclusivity provision allowed these extensions regardless of the outcome of the trial; that is, they were not contingent on labeling changes for pediatric use. Notably, the provision was not a patent term

extension; rather, it operated by extending any existing deferrals of FDA approval of generic entry.

Studies Addressing Primary Outcomes of Pediatric Exclusivity

After the pediatric exclusivity provisions were enacted, numerous pharmaceutical manufacturers initiated trials of their drugs in pediatric patients (Roberts et al. 2003). By 2007, more than three hundred pediatric studies had addressed efficacy/safety (25%), pharmacokinetics/safety (30%), pharmacokinetics/pharmacodynamics (20%), and safety alone (14%) (Milne 2002). The FDA-approved labeling changes for pediatric use affected more than 115 products and included new or revised pediatric information—such as new dosing, dosing changes, or pharmacokinetic information—new and/or enhanced safety data, information on lack of efficacy, new formulations, and dosing instructions extending the age limits in pediatric populations (Rodriguez et al. 2008). According to one report, nearly all drugs evaluated in exclusivity-inspired pediatric research had no adverse events necessitating enhanced adverse event monitoring (Smith et al. 2008).

Other studies describing outcomes from pediatric exclusivity trials, however, have raised concerns about the implementation of the incentive. First, studies examined the cost of the program. Critics charged that the six-month exclusivity period overcompensated manufacturers (Public Citizen 2001). An economic study of trials performed from 2002 to 2004 comparing predicted trial costs (e.g., contract research organization costs, per-patient site costs, and central laboratory costs) and calculating revenues (from sales audit data) found that the median cost to the drug manufacturer was $12 million (range, $5 million to $44 million) and the median net economic benefit to the manufacturer was $134 million (range, −$9 million to $508 million), a ratio of just over 10 to 1 (Li et al. 2007). While blockbuster drugs earned a high rate of return, most products in the cohort realized a much lower rate of return. A similarly designed study of nine antihypertensive drugs (including twenty-four clinical study reports) found that the median ratio of net economic return to cost was 17 to 1 (range 4–64.7 to 1) (Baker-Smith et al. 2008). In that analysis, the labels of seven of the nine products were changed as a result of the pediatric exclusivity trials. By contrast, another published

report concluded that analyses overestimated the return on pediatric trial investment by not taking into account some of the costs, such as the expense of producing pediatric drug formulations, although this study was based on interviews with interested parties (Milne and Bruss 2008). Using internal data provided by drug manufacturers (which cannot be confirmed), another study reported that pediatric trials have been increasing in length and complexity (Milne and Faden 2007).

Second, studies have raised concerns about the program's impact on public health. A descriptive study of drugs granted pediatric exclusivity through 2006 found that the drugs most frequently used by children were underrepresented in the pediatric exclusivity studies. Rather, most pediatric exclusivity studies were of drugs popular among adults (Boots et al. 2007). The second study, a cross-national comparison of drug labeling for pediatric patients, found that more drug labels addressed patients under age twelve in the United States than in the United Kingdom, Australia, and New Zealand (where no similar incentive provisions exist), although there were no significant differences among the countries in the proportion of drugs labeled for children under six years, under two years, and under one month of age (Grieve et al. 2005). The authors concluded that the pediatric exclusivity provision prompted trials mainly in slightly older pediatric patients.

Other studies examined the trials' quality and publication rates of pediatric drug studies. An in-depth case study of pediatric trials for hypertensive disease found important methodological flaws leading to results showing no statistically significant dose response, even though the agents were known to be effective in adults (Benjamin et al. 2008). A cross-sectional cohort study found that only 113 of the 253 (45%) pediatric studies performed from 1998 to 2004 were published in peer-reviewed journals (Benjamin et al. 2006). The lack of publication of completed trials may be a signal of reduced quality and prohibits an independent evaluation of the data.

Conclusions and Recommendations for Future Research on Pediatric Exclusivity

Since the pediatric exclusivity incentive was enacted, hundreds of pediatric trials have been performed, leading to some useful label changes. Nonetheless, studies of varying methodological rigor (see table 5) have questioned the quality of these trials, the cost of the program, and the impact of the pediatric exclusivity extension on public health outcomes.

TABLE 5
Studies Evaluating the Impact of the Pediatric Exclusivity Provision on Drug Development

Author(s)	Study Design	Summary of Results
FDA 2001	Descriptive review of studies requested and completed for pediatric exclusivity (1998–2000).	In less than 3 years, more than 58 pediatric studies were conducted, study reports submitted, and exclusivity granted to 25 drugs. Expected cost was about $700 million per year; potential savings "substantial" but not quantified. Methodological comments: Moderate value. Comprehensive look at early implementation, with some efforts to calculate cost-effectiveness.
Milne 2002	Survey of manufacturers involved in first 40 requests to perform pediatric exclusivity trials (response rate: 25/40, 63%).	Reported average of almost 3 clinical studies per product, trial costs average $3.9 million (min/max range: $0.5 million to $20 million), average 22.8 months to perform trials. Methodological comments: Low value. Qualitative insights into manufacturers' responses to the incentive. High risk of response bias, no statistical analyses done, and list of questions/respondents not provided.
Roberts et al. 2003	Descriptive review of labeling changes for drugs granted pediatric exclusivity (1998–2002).	53 drugs were granted pediatric exclusivity, and 33 drug products have new labels with pediatric information. Observations for 7 (21%) led to major adjustments in the dosing instructions. Methodological comments: Moderate value. High-quality descriptive study; no data on actual outcomes.
Grieve et al. 2005	Comparison of pediatric licensing status for drugs receiving pediatric exclusivity in U.S. (79 drugs, 1997–2003) that were also licensed in UK, Australia, and New Zealand (60/79, 76%).	In U.S., more drugs approved for children aged 6 to 12, but no significant differences for children < 6 years, < 2 years, and < 1 month old.

Continued

TABLE 5—*Continued*

Author(s)	Study Design	Summary of Results
		Methodological comments: Moderate value. High-quality cross-national comparison, potential for confounding.
Benjamin et al. 2006	Cohort study of all trials conducted for pediatric exclusivity (1998–2004), evaluating publication of the main study results in a peer-reviewed journal.	Of the 100 clinical trials associated with a key labeling change, only 37 were published. Of the 48 trials that did not result in a labeling change, only 19 (40%) were published. Efficacy studies and those with a positive labeling change were more likely to be published.
		Methodological comments: High value. Comprehensive study of an important issue related to pediatric exclusivity studies.
Milne and Faden 2007	Survey of 28 companies involved in pediatric exclusivity trials in 2002/2003 (response rate: 17/28, 61%).	Eightfold increase in the overall mean of self-reported costs for completing a pediatric exclusivity clinical trial. Drug sponsors find the exclusivity incentive attractive.
		Methodological comments: Low value. Limited survey subject to response bias.
Boots et al. 2007	Categorization of drugs granted pediatric exclusivity (1998–2006) and description of trends in pediatric and adult drug use.	Drugs granted pediatric exclusivity tended to be used rarely by children, while drugs frequently used by children were underrepresented in pediatric exclusivity studies.
		Methodological comments: Moderate value. Descriptive comparisons with no statistical testing done.
Li et al. 2007	Economic analysis of studies submitted for pediatric exclusivity (2002–2004). For each product, estimated the net economic return to industry.	The median cost per agent was $12.3 million (range, $5 million to $44 million), compared with median net economic benefit of $134 million (range, −$9 million to $508 million), for a ratio of about 10 to 1.

Continued

		Methodological comments: High value. Economic values derived using independent, well-described techniques; sensitivity analyses performed.
Smith et al. 2008	Descriptive review of outcomes from 67 drugs with safety concerns that were granted pediatric exclusivity (1998–2007).	The majority of drugs given exclusivity had no adverse events of a frequency or severity that prevented the Pediatric Advisory Committee (PAC) to return the drugs to routine adverse event monitoring. Methodological comments: Moderate value. Report of regulatory action, not a study of prescribing practices or clinical outcomes.
Baker-Smith et al. 2008	Economic analysis and descriptive review of clinical trials for 9 antihypertensive drugs submitted under the pediatric exclusivity provision (1997–2004).	An average of 2 studies per drug was performed, including at least 1 pharmacokinetic study and a safety and efficacy study. The median cost per agent was $6 million (range $4 million to $14 million), and the revenue-to-cost ratio was about 17 (range 4 to 65). Methodological comments: Moderate value. Similar methodology to Li et al., although in a smaller sample.
Rodriguez et al. 2008	Descriptive review of studies and labeling changes for drugs granted pediatric exclusivity (1998–2005).	They reported features of 250 studies conducted for 108 products. Methodological comments: Moderate value. See prior Roberts et al. study.
Benjamin et al. 2008	Descriptive review of a subset of pediatric exclusivity trials done for antihypertensive drugs (1998–2005).	Trials done for antihypertensive medications showed poor dose selection, lack of attention to pharmacodynamic differences in study populations, and lack of pediatric formulations. Methodological comments: Moderate value. In-depth descriptive study of a subset of drugs.

The collateral effects of the pediatric exclusivity provision have not been investigated in any well-controlled trials. For example, the six-month incentive may have harmful effects in the adult population from reduced medication adherence linked to the extra six months of elevated prices. In the case of atorvastatin (Lipitor), the manufacturer completed the necessary pediatric study to receive the six-month pediatric exclusivity extension for this costly cholesterol-lowering medication used widely by adults with coronary vascular disease. Few pediatric patients, however, require therapy with atorvastatin, and no studies suggest that atorvastatin provides additional benefit for pediatric patients over other cholesterol-lowering drugs in the same class. In contrast, in adult patients, atorvastatin has been shown to be specifically useful in high-risk patients who require LDL cholesterol lowering that cannot be achieved with other statins. The costs of the six-month pediatric exclusivity extension will fall nearly exclusively on those patients or their insurers. No studies have quantified how adherence to costly essential medications in the secondary adult market is affected by the six-month exclusivity extension.

Other potential collateral effects of pediatric exclusivity also bear investigation. Without comprehensive information about changes in pediatric prescription drug rates before and after these studies, it is hard to know the true impact of the pediatric exclusivity incentive. Therefore, it would be useful to study how changes in pediatric labeling affect drug use rates and clinical outcomes in children. It might also be useful to model alternatives to the pediatric exclusivity incentive. Direct grant funding of necessary trials may be more efficient than providing market exclusivity as a way of promoting clinical trials in this area. In the past, the National Institutes of Health have supported research to answer specific public health questions in high-risk populations. To provide additional incentives to manufacturers, Congress could enact a direct bonus of double the cost of the clinical trials attached to their complete execution. Testing such alternative mechanisms in a limited sample of commonly used pediatric drugs might require only a small amount of additional funding.

Summary and Future Directions

All four legislative programs discussed in this analysis have been the subject of studies addressing their impact and public health significance.

In general, most such studies are descriptive, such as those that chart the number of pediatric studies performed to earn the six-month pediatric exclusivity incentive. Fewer studies use comparators, such as experiences in other jurisdictions or fields, or other observational study techniques that account for confounding. No statute requires organizing the output from these statutes into transparent databases that can then be evaluated by government regulators as well as interested independent researchers, which hampers the overall quality of the policy analysis.

The results of some of the descriptive studies have been cited to validate these programs' success, but such results can paint incomplete pictures of the legislation's impact. For example, in the case of Bayh-Dole, other important factors occurring around the same time can also explain a rise in academic patenting in the biological sciences, including advances in biochemistry and DNA sequencing, U.S. Supreme Court decisions that broadened the range of patentable subject matter in the biological sciences, and regulatory changes that made it easier for inventors to patent their discoveries. In the case of the Orphan Drug Act, analyzing the number of new drugs for indications that are subsets of larger disease entities (e.g., "anemia in end-stage renal disease" for epoetin), as opposed to diseases in which the full manifestation of the disease is rare (e.g., Gaucher's disease), and analyzing the extent of off-label use of orphan drugs after their development may help give a better sense of how many drugs would have been developed without the legislation in place. Plans to evaluate the use of orphan drugs and their public health effects after initial FDA approval should be outlined in such legislation and should be the responsibility of manufacturers who receive the generous financial incentives offered.

Further investigation is needed of each of these incentive systems. Well-controlled analyses of these market exclusivity incentives would be preferred, although such work in health policy can be complicated and resource intensive (Jaffe 1999). Still, sometimes even limited data—such as anecdotal reports or simple post hoc analyses—can be useful in driving policy and measuring the changes emerging after the enactment of a legislative program. For example, the pediatric exclusivity provision was initially found to be of marginal utility in encouraging needed studies and was revised to permit greater flexibility in the types of drugs eligible for the incentives after five years. In this case, salutary policy changes were made without rigorous data in hand.

This analysis does not reach the conclusion that these legislative programs were misdirected or should not have been enacted. In fact, the

data show that important gains have emerged related to the incentives. Still, two main themes emerge from this review for scientists, health services researchers, and policymakers in this field. First, simply providing market exclusivity incentives to achieve a particular outcome cannot prevent misuse. Each program critically lacked a mechanism to moderate overcompensation that might lead to undesirable secondary consequences from cross-subsidizations. Second, there should be a rigorous, prospective, and independent plan for evaluating the results and the real potential to modify the incentive program to account for emerging trends in implementation.

The Downside of Market Exclusivity Incentives

Each incentive program reviewed here can point to certain claims supporting its effectiveness. Certainly, a number of important drugs for rare diseases have been developed since 1983, and the Orphan Drug Act and OOPD assisted their development to varying degrees. In the case of Bayh-Dole, there are many positive examples of technology transfer leading to scientific breakthroughs or useful drug development. Hatch-Waxman's 180-day exclusivity period has been a sought-after prize, as demonstrated by its recent rise in popularity, drawing drug manufacturers to the generic drug market.

These descriptive outcomes are insufficient, however, for judging the overall success of these programs, including their efficiency and cost-effectiveness. In fact, each of these programs has generated undesired responses. In the case of Hatch-Waxman, the 180-day exclusivity period has generated settlement agreements that benefit brand-name and generic drug manufacturers at the expense of patients and payers, by delaying the entry of generic drugs. In addition to misuse, unintended consequences with substantial public health importance have emerged from each market exclusivity incentive program (Kesselheim 2010b). Bayh-Dole may help commercialize some discoveries, but the impact of patenting and commercialization may slow other aspects of the research process or change the focus of university-based basic science, to the detriment of innovation more broadly.

Acknowledging the diversity in responses helps place these market exclusivity incentives in their proper light and suggests some lessons for similar future programs. Using market exclusivity as a tool to promote drug development allows the government to subsidize a certain goal

without directly allocating its resources, with the costs borne by patients and third-party payers. But such indirect mechanisms can lead to wasting limited resources and even gaming of the system. Thus, alternative strategies should be considered for promoting drug development, such as more transparent and direct resource allocations. This strategy, too, has potential limitations, because regulators might not know best where to optimally allocate resources. If alternative mechanisms of support are not used, policymakers should strive to construct market exclusivity incentives narrowly and consider linking the incentives directly to the public health outcomes (Hollis and Pogge 2008). For future programs that do choose to use market exclusivity to promote pharmaceutical development, a reasonable first step might be to organize limited pilot programs in controlled environments in which such analyses can be more easily conducted and to compare the results with those of pilot programs that use other incentive structures.

Periodic Evaluation

The efforts to collect empirical data regarding the impact of the legislative programs in this review have been insufficient in important ways. Many of the studies discussed were patched together from data from disparate sources or were complicated by potential conflicts of interest. For example, the information about Bayh-Dole came from the AUTM, which has a conflict of interest by virtue of being a trade association of technology transfer offices. Formal research into a market exclusivity incentive program's effectiveness should be organized prospectively and should be undertaken by experts independent of connections to the organizations receiving the benefits of the incentive. In the case of Bayh-Dole, the Department of Commerce or the Government Accountability Office may be in a less conflicted position to conduct needed reviews.

Fortunately, federal support for science policy studies may be improving. The U.S. Office of Science and Technology Policy has made it a priority to develop tools and benchmarks to measure innovative output from policy changes (Office of Science and Technology Policy 2008). In the past, fears concerning trade secrets and confidentiality have hampered the transparent presentation of data collected by government offices, but these concerns should be manageable (National Research Council 2010). Indeed, the public availability of data relating

to outcomes should be a requirement for involvement in any public-sponsored incentive program.

Conclusion

This review of U.S. legislative programs that use market exclusivity incentives to promote public health outcomes in the field of pharmaceutical development shows that such programs have demonstrated success in producing important medical advances. These incentive programs, however, have also been characterized by misuse and may contribute to harmful secondary consequences in related markets. The suboptimal implementation of these incentives has important public health implications because inappropriate or undeserved exclusivity in the pharmaceutical market can lead to excessive health care spending and reduced patient access to essential drugs. Programs seeking to encourage the practical application of university research and to develop incentives for privately funded research and development to produce drugs, devices, and biologics should be directly linked to the intended public health outcome. In addition, policymakers need to approach these incentive systems with a more critical and evaluative perspective through better pilot testing of alternatives and ongoing analysis of newly adopted policies.

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